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## Case-control study of leukaemia and non-Hodgkin's lymphoma in children in Caithness near the Dounreay nuclear installation

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### Abstract

**Objective**—To examine whether the observed excess of childhood leukaemia and non-Hodgkin's lymphoma in the area around the Dounreay nuclear installation is associated with established risk factors, or with factors related to the plant, or with parental occupation in the nuclear industry.

**Design**—Case-control study.

**Setting**—Caithness local government district.

**Subjects**—14 cases of leukaemia and non-Hodgkin's lymphoma occurring in children aged under 15 years diagnosed in the area between 1970 and 1986 and 55 controls matched for sex, date of birth, and area of residence within Caithness at time of birth.

**Main outcome measures**—Antenatal abdominal x ray examination; drugs taken and viral infections during pregnancy; father's occupation; father's employment at Dounreay and radiation dose; distance of usual residence from the path of microwave beams, preconceptional exposure to non-ionising radiation in the father; and other lifestyle factors.

**Results**—No raised relative risks were found for prenatal exposure to x rays, social class of parents, employment at Dounreay before conception or diagnosis, father's dose of ionising radiation before conception, or child's residence within 50 m of the path of microwave transmission beams. Results also proved negative for all lifestyle factors except an apparent association with use of beaches within 25 km of Dounreay. However, this result was based on small numbers, arose in the context of multiple hypothesis testing, and is certainly vulnerable to possible systematic bias.

**Conclusion**—The raised incidence of childhood leukaemia and non-Hodgkin's lymphoma around Dounreay cannot be explained by paternal occupation at Dounreay or by paternal exposure to external ionising radiation before conception. The observation of an apparent association between the use of beaches around Dounreay and the development of childhood leukaemia and non-Hodgkin's lymphoma might be an artefact of multiple testing and influenced by recall bias.

### Introduction

In 1988 the Committee on the Medical Aspects of Radiation in the Environment (COMARE) published the report of its investigation into the incidence of leukaemia and non-Hodgkin's lymphoma in young people in the area around the Dounreay nuclear installation in Caithness during 1968-84.<sup>1</sup> The committee concluded that the apparent excess incidence within the area 25 km from the plant during 1979-84 justified further study. The case-control study of all cases of leukaemia and non-Hodgkin's lymphoma

occurring in children aged under 15 in Caithness during 1968-86 reported in this paper forms one part of the series of investigations recommended by the committee. A follow up study of incidence of cancer in birth and school cohorts in the Dounreay area will be reported later.

Because of the small number of cases the study was not expected to provide insights into the general aetiology of childhood leukaemia; the primary objective was to determine the extent to which the excess incidence of leukaemia and non-Hodgkin's lymphoma occurring within 25 km of the plant might be explained by risk factors suggested by earlier studies. These factors include maternal exposure to x rays during pregnancy<sup>2</sup> and aspects of parental occupation, including paternal exposure to relatively small doses of ionising radiation before conception of the child.<sup>3</sup> Other risk factors examined, such as patterns of viral infection in the mother and certain aspects of lifestyle, are necessarily somewhat speculative.

Although the main emphasis of the study was to use case-control methods to investigate cases of leukaemia and non-Hodgkin's lymphoma occurring within 25 km of Dounreay, it was recognised that possible risk factors relating to employment in particular would be present among people living in a wider area of Caithness. For this reason the study was extended to include all cases of childhood leukaemia and non-Hodgkin's lymphoma occurring within Caithness from 1968 to 1986. Results are presented separately for the 25 km zone and for the whole of Caithness.

### Subjects and methods

All registered cases of leukaemia and non-Hodgkin's lymphoma in children resident in Caithness during 1968-86 were included in the study, and we selected controls who were matched with case children for sex and date of birth. The controls were also matched by mother's area of residence at birth, and for this purpose Caithness was divided into two zones: (a) the area lying within 25 km of the Dounreay nuclear installation and (b) the remainder of Caithness. For each case the birth register was used to select four controls for whom the mother's zone of residence at birth corresponded with that of the case child. The controls selected were those meeting the matching criteria with dates of birth closest to the dates of birth of the index cases.

Two cases in children who were resident within 25 km of the Dounreay nuclear installation at the time of diagnosis were born outwith Caithness. To permit analysis of risk factors relating to the period before birth four controls were selected for these two cases from the registration districts of birth. An additional four matched controls with mothers who were resident in the inner 25 km zone at the time of birth were also

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selected for these two cases. These further controls were used only in the analysis of those risk factors which related to the period after birth. The names and dates of birth of the parents of each case and control were determined by a search of the public marriage and birth records held by the General Register Office for Scotland and the Office of Population Censuses and Surveys. The current addresses of each control and his or her parents were determined from the records of health boards' primary care divisions after a search of the NHS central register. If, and only if, their family practitioner agreed to an approach, these parents were asked by letter if they wished to participate in the study. Control children who had died before the date of diagnosis for the index case were omitted from the study. If a control child had left the Caithness area before the date of diagnosis for the matched case all results for that control relating to the period after birth were excluded from the analysis.

Information was collected from each parent by experienced interviewers with a detailed and structured questionnaire. Respondents were asked for signed permissions for access to their medical records and to data (including information on external radiation dose) held by current and former employers. Detailed information was collected for the child and for each parent on all places of residence, on their medical history with particular reference to exposure to x rays, and on any viral infections. A detailed pregnancy history was collected in respect of the index child, and all vaccinations and immunisations were recorded. An exhaustive occupational history was obtained for each parent, which included information on parental exposures to radiation and particular chemicals. When possible, information relating to the period of pregnancy with the index child was extracted from medical records. It included maternal exposure to x rays, viral infections, drug treatments, and complications of pregnancy. All parents included in the study were cross matched against the occupational records held by the United Kingdom Atomic Energy Authority at Dounreay and Harwell and by HMS Vulcan, Caithness, to determine periods of employment at nuclear installations in Caithness and elsewhere in the United Kingdom. We obtained records of annual radiation dose for the parents who were so employed. In addition, records of monthly radiation dose were obtained in respect of the two years preceding the birth of the child. Information provided by the United States naval authorities permitted the shortest distances from the place of residence at the time of diagnosis to the path of transmission beams of the microwave transmitters in the Thurso area to be calculated from grid references. Information was also collected on aspects of lifestyle of both the child and the parents, including diet and the use of local beaches up to the date of diagnosis in the cases.

TABLE 1—Cases eligible for inclusion in study

Case No	Place of birth*	Place of diagnosis*	Year of diagnosis	Included in employment record and birth certificate study	Included in questionnaire and medical record study
1	≥25 km	≥25 km	1969	Yes	Yes
2	≥25 km	≥25 km	1969	Yes	Yes
3	<25 km	<25 km	1970	Yes	No
4	Outwith Caithness	≥25 km	1970	No	No
5	≥25 km	≥25 km	1974	Yes	Yes
6	≥25 km	≥25 km	1979	Yes	Yes
7	≥25 km	≥25 km	1979	Yes	Yes
8	<25 km	<25 km	1980	Yes	Yes
9	<25 km	<25 km	1980	Yes	Yes
10	<25 km	<25 km	1980	Yes	Yes
11	<25 km	<25 km	1981	Yes	Yes
12	<25 km	<25 km	1983	Yes	No
13	Outwith Caithness	<25 km	1983	Yes	Yes
14	Outwith Caithness	<25 km	1986	Yes	Yes

\*<25 km or ≥25 km from Dounreay or outwith Caithness.

Some parents of control children were not approached for an interview at the specific request of their general practitioner, and other parents subsequently refused to be interviewed after an authorised approach had been made. When fewer than two original controls were available for a particular case substitute controls were selected according to the same procedure as before. Interviews were performed with parents of the substitute controls, but to guard against the possibility of systematic bias information on external radiation doses and employment history before the birth of the child was obtained for all cases and all original controls, irrespective of whether an interview subsequently took place. No substitute controls were required for cases in children living within 25 km of Dounreay at the time of diagnosis.

The study should therefore be regarded as two separate studies with overlapping controls—the first based on birth certificates and the employment records of the nuclear industry and the second on questionnaire information and medical records.

Estimates of odds ratios,<sup>4</sup> which approximate closely to relative risks, were calculated with the conditional logistic regression module of the EGRET computer package.<sup>5</sup> Because of the small numbers eligible for inclusion in the study problems of analysis existed when there was concordance between cases and controls within the matched sets. When as a consequence the number of cases contributing to the estimation of the relative risk was three or fewer Fisher's exact test was used to test a null hypothesis of homogeneity and the result of this is shown as a p value. The conditional logistic regression was carried out within matched sets of cases and controls and Fisher's exact test on unmatched cases and controls. Reported relative risk estimates are for the presence of each factor compared with its absence.

The cases included in the study have been the subject of intensive investigation by the Committee on the Medical Aspects of Radiation in the Environment in respect both of completeness of recording and of accuracy of diagnosis. One conclusion in the committee's report was that with time and with changes in diagnostic practice uncertainties existed in discriminating between leukaemia and non-Hodgkin's lymphoma. For this reason the results of this study are shown for leukaemia and non-Hodgkin's lymphoma combined. The results of the study based on birth certificates and employment records of the nuclear industry are shown separately from those of the study based on information from the questionnaire and medical records.

#### COMPLETENESS OF RESPONSE

Fifteen cases of leukaemia and non-Hodgkin's lymphoma were registered in Caithness during 1968-86 in young people aged below 25; one case registered within the 25 km zone around Dounreay was in a subject aged 23 years at diagnosis. The subject was born in 1960 and was excluded from the study because of difficulties in obtaining reliable information about the preconceptional and early childhood periods after such an extended time interval. The 14 other cases were all aged under 15 at the time of diagnosis.

Eight cases were in children resident within the 25 km zone around Dounreay at the time of diagnosis. In one the diagnosis was in 1970 and in the remaining seven during 1979-86. These seven cases provide the focus of concern in the committee's report.<sup>1</sup> Two of these seven cases were in children born outwith the Caithness area and the remaining five were in children born within the 25 km zone.

In four of the six cases in children resident in the area of Caithness outwith the 25 km zone diagnosis was during 1968-78. One of these was in a child born outwith Caithness. To respect the specific wishes of

TABLE II—Numbers of cases and controls included in study

	No of cases eligible for inclusion	No included in employment record and birth certificate study		No included in questionnaire and medical record study			
		Cases	Controls	Cases	Original controls	Replacement controls	Total controls
Total	13	13	47	11	26	10	36
Diagnosis and birth within 25 km zone	6	6	23	4	14	0	14
Diagnosis within 25 km zone and birth outwith Caithness	2	2	4	2	6	0	6
Diagnosis outwith 25 km zone and birth within Caithness	5	5	20	5	6	10	16

TABLE III—Numbers of cases and controls and odds ratio or Fisher's exact p value, by paternal occupation recorded on birth certificate

Father's occupation or industry	Cases		Controls		Odds ratio	95% Confidence interval	Fisher's exact p value
	Total	Positive	Total	Positive			
<i>Resident &lt;25 km from Dounreay at diagnosis</i>							
Dounreay	8	2	25	12	0.38	0.06 to 2.34	*
Farming	8	0	25	3	0	*	0.42
Fishing	8	1	25	2	2.45	0.14 to 42.59	*
<i>Resident anywhere in Caithness at diagnosis</i>							
Dounreay	12	3	41	15	0.58	0.13 to 2.59	*
Farming	12	0	45	5	0	*	0.29
Fishing	12	2	41	5	2.03	0.25 to 16.46	*

\*Not calculated.

TABLE IV—Numbers of cases and controls and odds ratio or Fisher's exact p value by paternal employment in nuclear industry at conception of child and estimated ionising radiation doses before conception

	Cases		Controls		Odds ratio	95% Confidence interval	Fisher's exact p value
	Total	Positive	Total	Positive			
<i>Resident &lt;25 km from Dounreay at diagnosis</i>							
Father employed in nuclear industry at conception	8*	2	25†	12	0.38	0.06 to 2.34	‡
Father's radiation dose (mSv):							
Lifetime dose ( $\geq 100$ v $< 100$ )	8	0	25	1	0	‡	0.76
Six months before conception ( $\geq 10$ v $< 10$ )	8	1	25	0	$\infty$	‡	0.24
<i>Resident anywhere in Caithness at diagnosis</i>							
Father employed in nuclear industry at conception	12*	3	41†	15	0.58	0.13 to 2.59	‡
Father's radiation dose (mSv):							
Lifetime dose ( $\geq 100$ v $< 100$ )	12	0	45	1	0	‡	0.79
Six months before conception ( $\geq 10$ v $< 10$ )	12	1	45	0	$\infty$	‡	0.21

\*Fathers of three cases who were not employed in the nuclear industry before birth of child were employed before diagnosis.

†Fathers of three controls who were not employed in the nuclear industry before birth of child were employed before diagnosis of matched case.

‡Not calculated.

TABLE V—Numbers of cases and controls by estimated ionising radiation dose before conception

Father's radiation dose before conception	Resident <25 km from Dounreay at diagnosis		Resident anywhere in Caithness at diagnosis	
	Cases	Controls	Cases	Controls
Total lifetime dose (mSv):				
None	6	17	9	33
1-4.9	2	6	3	9
5.0-9.9	0	1	0	2
$\geq 10.0$	0	1	0	1
Total	8	25	12	45
Dose six months before (mSv):				
None	6	19	9	35
0.1-4.9	1	5	2	8
5.0-9.9	0	1	0	1
$\geq 10.0$	1	0	1	1
Total	8	25	12	45

TABLE VI—Numbers of cases and controls resident <25 km from Dounreay at time of diagnosis by distance from place of residence to transmission path of microwave beams from United States naval communications transmitters in Thurso area

Distance to transmission path (m)	Cases		Controls	
	Cases	Controls	Cases	Controls
<100	0	0	0	0
100-200	0	0	0	0
200-300	0	0	0	0
300-400	1	0	0	0
400-500	2	1	0	0
500-600	0	1	0	0
600-700	1	1	0	0
700-800	0	2	0	0
800-900	0	0	0	0
900-1000	1	3	0	0
$\geq 1000$	3	19	0	0

Kolmogorov-Smirnov D=0.39, p>0.10.

parents no information about this case has been included in the study.

Thirteen cases were therefore admitted to the study; table I shows for each the areas of birth and diagnosis, the year of diagnosis, and whether the case was included in the employment record and birth certificate study and the questionnaire study. Table II shows the response rates for the two parts of the study.

Information on parental occupation, age of parents at the time of the child's birth, and place of birth of mother was obtained for all 13 cases. For one case in a

child born within Caithness but outwith the 25 km area around Dounreay the father could not be traced. Information from questionnaires was available for six of the eight cases in children resident within the 25 km zone at the time of diagnosis and for all five in children resident in the remainder of Caithness. In one of the two cases for which no information was available the parents declined to participate in the study, and in the other no approach was made to the parents, at the specific request of the family practitioner. Information from questionnaires was obtained for 20 controls matched to the six cases in children resident in the 25 km zone around Dounreay at time of diagnosis and for 16 controls matched to the five cases in children resident in the remainder of Caithness. No replacement controls were required for any of the cases in children resident within 25 km of Dounreay at the time of diagnosis. Ten of the controls selected for cases resident in the remainder of Caithness were replacements.

## Results

### EMPLOYMENT RECORD AND BIRTH CERTIFICATE STUDY *Paternal occupation and employment at Dounreay*

Information on parental occupation was obtained from birth certificates and from the computer files of workers employed at Dounreay and elsewhere in the nuclear industry. Information available from questionnaires was used as confirmation. Table III shows the paternal occupation for cases and controls at the time of birth of the child for the main industrial groups found in the Caithness area. For three cases the fathers were employed in the nuclear industry at the time of the birth of the child (odds ratio 0.58, 95% confidence interval 0.13 to 2.59). One of them was described as an electrician, one as a process worker, and one as a charge hand. All these fathers were employed at Dounreay at the time of conception of the child and two were fathers of cases resident within 25 km of Dounreay at the time of diagnosis (odds ratio 0.38, 0.06 to 2.34). No significantly raised risk was associated with employment in farming or fishing (table III). Information derived from the occupational records was used to identify periods of employment in the nuclear industry of fathers of cases and controls before conception of their children. No raised risks were observed in respect of these periods of employment (table IV). None of the fathers of cases had an accumulated external ionising radiation dose >100 mSv before conception of the child (table V); the fathers of three cases who were employed in the nuclear industry each had a lifetime dose <50 mSv (40 mSv, 29 mSv, and 17.4 mSv respectively). One father of a case had a dose >10 mSv (13.6 mSv) in the six months before conception; the two other fathers had doses of 3.7 mSv and 0.7 mSv respectively. No significant differences were observed between cases and controls with respect to these external radiation doses.

### *Exposure to non-ionising radiation*

Table VI shows, for the 25 km zone alone, the shortest distance between the place of residence of cases at diagnosis and of their controls and the

transmission paths of United States naval communications transmitters situated at Murkle, Cairnmore Hillock, and Forss. These transmitters emit a line of sight beam in the frequency range 7735.5-8340.0 MHz and have a reported beam width of 2°, giving a maximum area of putative risk of 50 m on either side of the transmission path. In neither cases nor controls was the place of residence within this area. A Kolmogorov-Smirnov test showed no significant difference between cases and controls in their cumulative distributions of distance from the place of residence to the pathway of the beam.

#### Place of birth of mother, age of parents, social class

No significantly raised risks were observed in relation to the mother's or father's age at time of birth of the child or to the mother's place of birth outwith Caithness (table VII). For the cases in the 25 km zone and for those in Caithness as a whole there was a non-significant excess of cases in children whose parents were classified as being in social classes III manual, IV, or V at the time of the child's birth.

TABLE VII—Numbers of cases and controls and odds ratio or Fisher's exact *p* value by parental age (years), mother's place of birth, and social class

Suspected risk factor	Cases		Controls		Odds ratio	95% Confidence interval	Fisher's exact <i>p</i> value
	Total	Positive	Total	Positive			
<i>Resident &lt;25 km from Dounreay at diagnosis</i>							
Mother born outwith Caithness	8	5	27	16	0.95	0.13 to 6.77	*
Mother's age (≥25 v <25)	8	4	25	14	0.78	0.16 to 3.81	*
Father's age (≥25 v <25)	8	6	24	21	0.26	0.02 to 3.26	*
Social class†	8	0	26	7	0	*	0.12
<i>Resident anywhere in Caithness at diagnosis</i>							
Mother born outwith Caithness	13	7	46	19	1.70	0.35 to 8.20	*
Mother's age (≥25 v <25)	13	7	42	19	1.40	0.40 to 4.89	*
Father's age (≥25 v <25)	12	9	38	28	0.96	0.20 to 4.49	*
Social class†	13	0	46	7	0	*	0.16

\*Not calculated.

†Of father at child's birth (I, II, III non-manual v III manual, IV, V).

TABLE VIII—Numbers of cases and controls and odds ratio or Fisher's exact *p* value by abdominal x ray exposure and drugs received during mother's pregnancy

Suspected risk factor	Cases		Controls		Odds ratio	95% Confidence interval	Fisher's exact <i>p</i> value
	Total	Positive	Total	Positive			
<i>Resident &lt;25 km from Dounreay at diagnosis</i>							
Abdominal x rays during pregnancy	5	0	19	1	0	*	0.79
Drugs received during pregnancy	5	3†	15	0	∞	*	0.01
Drugs received during labour	4	3	16	15	*	*	0.37
Pethidine received during labour	4	3	16	12	*	*	0.72
<i>Resident anywhere in Caithness at diagnosis</i>							
Abdominal x rays during pregnancy	7	0	31	2	0	*	0.66
Drugs received during pregnancy	7	3†	18	1	7.42	0.77 to 72.00	*
Drugs received during labour	6	4	28	22	*	*	0.44
Pethidine received during labour	6	4	16	11	1.14	0.10 to 13.27	*

\*Not calculated.

†One mother received lactulose and co-phenotrope, one penicillin, and one flurazepam and cimetidine.

TABLE IX—Numbers of cases and controls and odds ratio or Fisher's exact *p* value by eating habits and use of local beaches

Habit factor	Cases		Controls		Odds ratio	95% Confidence interval	Fisher's exact <i>p</i> value
	Total	Positive	Total	Positive			
<i>Resident &lt;25 km from Dounreay at diagnosis</i>							
Eating:							
Locally grown vegetables or fruit	6	2	18	11	0.38	0.06 to 2.28	*
Locally caught fish	6	3	18	12	0.50	0.07 to 3.37	*
Locally caught shellfish	6	0	18	4	0	*	0.29
Locally caught game	6	0	18	1	0	*	0.75
Playing on beach†	5	5	16	7	∞	*	0.04
<i>Resident anywhere in Caithness at diagnosis</i>							
Eating:							
Locally grown vegetables or fruit	11	6	31	16	1.16	0.32 to 4.16	*
Locally caught fish	11	6	31	14	1.46	0.32 to 6.72	*
Locally caught shellfish	11	1	31	5	0.42	0.04 to 4.60	*
Locally caught game	11	0	31	1	0	*	0.74
Playing on beach†	9	5	30	8	∞	*	0.12

\*Not calculated.

†Within 25 km of Dounreay.

#### QUESTIONNAIRE AND MEDICAL RECORDS STUDY

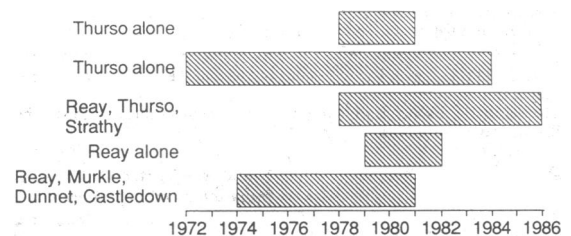
##### Antenatal exposure to x rays

Information on antenatal exposure to x rays was derived from the questionnaire and verified when possible from the antenatal medical records. No mother of a case was recorded as having received x rays antenatally according to either the questionnaire or the medical records. x Rays were received antenatally by the mothers of two controls according to the antenatal records (table VIII).

In three of the five cases in children resident in the 25 km zone for whom information was available from medical records drugs had been prescribed during their mother's pregnancy compared with none in the controls for whom equivalent information was available ( $p=0.01$ ). There was no consistent pattern in the drugs which were prescribed; one mother had received lactulose and co-phenotrope, one penicillin, and one flurazepam and cimetidine.

##### Aspects of lifestyle

No raised risks were observed in either those resident within the 25 km zone or in the study group taken as a whole in respect of consumption of locally grown vegetables, fish, game, or shellfish (table IX). Parents were asked detailed information about their children's use of local beaches. Information was recorded on which beaches were visited and on the years in which the child had played there. The results reported are for the use of beaches within 25 km of Dounreay. Of the five cases in children resident in the 25 km zone at the time of diagnosis for whom information was available, all were reported by both the mother and the father as using these beaches before diagnosis, both in 1979 and in 1980 (figure). When cases and controls were compared there was an excess incidence of use of the beaches by cases resident in the 25 km zone ( $p=0.04$ ).



Use of beaches within 25 km of Dounreay in five cases of leukaemia and non-Hodgkin's lymphoma diagnosed within the 25 km zone, 1972-86

##### Other risk factors

No viral infections during pregnancy were recorded in the medical records in respect of the mothers of any of the cases included in the study. In one case and nine controls the mothers were recorded on the questionnaire as having had a viral infection during pregnancy ( $p=0.26$ ); the case was in a child resident outside the 25 km zone (table X). No significantly raised risks were observed in either the group resident in the 25 km zone or the study group taken as a whole in respect of caesarean section, breast feeding, high birth weight (>3500 g), or smoking during pregnancy.

#### Discussion

In their case-control study of leukaemia and lymphoma among young people in west Cumbria Gardner *et al* observed higher relative risks in children whose fathers were employed at the Sellafield plant and, in particular, in those whose fathers had had high radiation dose recordings before their conception.<sup>3</sup> The Dounreay and Sellafield installations are the only nuclear reprocessing plants in Britain, and both have a reported excess of childhood leukaemia in their

TABLE X—Numbers of cases and controls and odds ratio or Fisher's exact *p* value by suspected prenatal and postnatal risk factors and vaccination of child

Suspected risk factor	Cases		Controls		Odds ratio	95% Confidence interval	Fisher's exact <i>p</i> value
	Total	Positive	Total	Positive			
<i>Resident &lt;25 km from Dounreay at diagnosis</i>							
Smoking during pregnancy	6	3	20	8	1.41	0.23 to 8.51	*
Caesarean delivery	6	0	20	2	0	*	0.58
Breast feeding	6	1	20	12	0.17	0.02 to 1.52	*
Birth weight ( $\geq 3500$ v $< 3500$ g)	6	0	20	4	0	*	0.32
Maternal viral infection in pregnancy	6	0	20	5	0	*	0.24
Child vaccinated before diagnosis	5	5	18	18	*	*	1.00
<i>Resident anywhere in Caithness at diagnosis</i>							
Smoking during pregnancy	11	5	35	16	1.03	0.26 to 4.12	*
Caesarean delivery	11	2	35	3	2.30	0.31 to 17.24	*
Breast feeding	11	2	35	14	0.33	0.06 to 1.76	*
Birth weight ( $\geq 3500$ v $< 3500$ g)	11	1	35	11	0.22	0.03 to 1.91	*
Maternal viral infection in pregnancy	10	1	30	9	0.35	0.04 to 3.09	*
Child vaccinated before diagnosis	9	9	30	30	*	*	1.00

\*Not calculated.

immediate surrounding areas,<sup>6-10</sup> which, in the view of the Committee on the Medical Aspects of Radiation in the Environment, seem unlikely to be the result of chance.<sup>1</sup> In view of the findings of Gardner *et al* there seems to be a prior hypothesis of a possible association between paternal employment at Dounreay and the development of leukaemia by their children, but no raised relative risks associated with such employment were observed in this study.

A particular focus of concern in the committee's report was the seven cases occurring between 1979 and 1986 in children resident in the 25 km zone around Dounreay. A primary objective of this study was to determine whether any of these cases could be explained by possible risk factors identified in earlier studies. Six of the fathers of these cases were not employed in the nuclear industry before conception of the child. Thus, although the results of the current study do not contradict the hypothesis developed by Gardner *et al*, this particular hypothesis clearly does not explain the excess incidence of childhood leukaemia and non-Hodgkin's lymphoma observed in the 25 km radius circle around Dounreay from 1979 to 1986. For example, the exclusion of the case occurring after 1979 in a child whose father was employed in the nuclear industry still leaves a significant excess incidence of childhood leukaemia and non-Hodgkin's lymphoma for 1979-86 (observed 6, expected 1.2;  $p=0.002$ ). Speculation in the press that the microwave transmitters in the Thurso area might be a source of risk in the development of childhood leukaemia was based on inconclusive results of studies in the United States.<sup>11,12</sup> The results of our study do not provide evidence to support this hypothesis as in none of the cases was the child resident in the reported area of putative risk at the time of diagnosis.

The results of this study suggest a possible association between the children's use of beaches and risk of leukaemia. This result differs from that found by Gardner *et al*, who reported no raised relative risk for children using beaches in Cumbria.<sup>1</sup> However, the results of the two studies in this respect are not comparable. In this study interviewers were able to determine the particular beaches used by the children. In contrast, the west Cumbria study did not attempt to differentiate between beaches close to the Sellafield plant and other beaches in Cumbria. In interpreting the result, consideration must be given to possible confounding factors and sources of bias. Residence in the immediate vicinity of one of the beaches within 25 km of Dounreay might be postulated as increasing the likelihood of a child visiting a beach to play. If the cases and controls differed in this respect then the higher proportion of cases reported to have used the beaches might simply reflect the geographical distribution of their places of residence. However, the proportion of cases and controls living within 1 km of a

beach were similar (four of five cases and 12 of 16 controls). The potential for interviewer bias was reduced in this study by using trained interviewers and a structured questionnaire, but recall of the parents of children with leukaemia or non-Hodgkin's lymphoma may have been influenced by media speculation about the role of local beaches as a potential route of exposure of children to radiation. It should also be noted that reliable information on the use of the beaches was not available for three of the eight cases in children resident within 25 km of Dounreay at the time of diagnosis. Furthermore, there was no prior reason for selecting use of beaches as a factor for testing in preference to any other possible risk factors relating to lifestyle. Thus the observation of a possible association between use of beaches and risk of leukaemia arose in the context of multiple testing. The observation that all five cases for whom information was available had used the beaches in the same two years may be of interest but without other evidence of possible sources of risk is inconclusive.

The main conclusion from this study is that the observed excess incidence of childhood leukaemia and non-Hodgkin's lymphoma in the area within 25 km of the Dounreay nuclear installation cannot be explained by any of the risk factors for which evidence has been adduced from earlier studies. In addition to paternal occupation, raised risk was previously found to be associated with maternal exposure to x rays during pregnancy<sup>3</sup> and with higher social class.<sup>13</sup> In this study in none of the cases had mothers received x rays during pregnancy and in all the cases the fathers were of social class III manual or below.

It must be emphasised that the results from such a small study cannot be used to refute claims of association with risk factors that have been based on studies carried out in other geographical areas. Thus the results of this study do not provide evidence that contradicts observations for west Cumbria of an association between the employment of fathers in the nuclear industry and the development of leukaemia or lymphoma in their children; they simply show that the excess incidence around Dounreay is not explained by such an association. Nor, on the other hand, should apparent disparities between the results of the west Cumbria study and those of this study be assumed to indicate that different explanations exist for the two observations of excess incidence. The causes of the excess incidence of leukaemia in children in the two areas might be the result of a complex multifactorial aetiology in which the effects of individual risk factors are multiplicative. Thus, for example, the excess incidence observed in the Sellafield area might be the result of the multiplicative effects of preconceptional exposure to radiation in fathers and some hitherto unrecognised risk factor or factors that are also present in the area around Dounreay. If preconceptional exposure to radiation in the father increased predisposition to developing childhood leukaemia then differences in the levels of exposure to other risk factors might be the crucial determinant of the extent to which leukaemia occurred in the respective populations of children.

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## Enteroviral RNA sequences detected by polymerase chain reaction in muscle of patients with postviral fatigue syndrome

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### Abstract

**Objective**—To determine the presence of enteroviral sequences in muscle of patients with the postviral fatigue syndrome.

**Design**—Detection of sequences with the polymerase chain reaction in a well defined group of patients with the syndrome and controls over the same period.

**Setting**—Institute of Neurological Sciences, Glasgow.

**Subjects**—60 consecutive patients admitted to the institute with the postviral fatigue syndrome who had undergone extensive investigation to exclude other conditions. 41 controls from the same catchment area without evidence of fatigue, all undergoing routine surgery.

**Main outcome measures**—Routine investigations, serological screen for antibodies to a range of viruses, and presence of enteroviral RNA sequences in muscle biopsy specimens.

**Results**—15 (25%) patients and 10 (24.4%) controls had important serological findings. 12 patients had neutralising antibody titres of  $\geq 256$  to coxsackieviruses B1-5 (six positive for enteroviral RNA sequences, six negative); three were positive for Epstein-Barr virus specific IgM (two positive, one negative). Six controls had similar neutralising antibody titres to coxsackieviruses (all negative); one was positive for Epstein-Barr virus specific IgM (negative); and three had titres of complement fixing antibody  $\geq 256$  to cytomegalovirus (all negative). Overall, significantly more patients than controls had enteroviral RNA sequences in muscle (32/60, 53% v 6/41, 15%; odds ratio 6.7, 95% confidence interval 2.4 to 18.2). This was not correlated with duration of disease, patient and age, or to raised titres of antibodies to coxsackieviruses B1-5.

**Conclusions**—Persistent enteroviral infection of muscle may occur in some patients with postviral fatigue syndrome and may have an aetiological role.

### Introduction

Patients with a protracted fatigue state after an acute, apparently viral infection (the postviral fatigue syndrome) may present to general practitioners, physicians, neurologists, or psychiatrists.<sup>1,3</sup> The fatigue is accompanied by myalgia, and most patients also have psychiatric symptoms, particularly depression and disturbance of sleep. About one third complain of palpitations or unsteadiness, or both. Physical signs, however, are inconsistent or absent, and routine laboratory test results are normal.<sup>3</sup>

The features of this disorder suggest that the fatigue is caused by involvement of both muscle and the central nervous system. There is some direct evidence of muscle damage as membrane abnormalities are detectable on single fibre electromyography.<sup>4</sup> In the few patients studied by magnetic resonance investigations unusually early intracellular acidosis out of proportion with the associated rise in high energy phosphates was reported on exercise. (D L Arnold *et al.*, abstract, third annual meeting of the Society for Magnetic Resonance in Medicine, New York, 1984.)<sup>5</sup> Muscle biopsy specimens may disclose moderate diffuse atrophy of type 2 fibres.<sup>6</sup>

Diagnosis and definition of this disease have been difficult, but we have now established a set of criteria, similar to those delineated in a recent working case definition,<sup>7</sup> except that the disease is diagnosed only in relation to an acute onset after a feverish illness. The postviral fatigue syndrome has many synonyms—for example, myalgic encephalomyelitis<sup>1</sup> and postviral epidemic neuromyasthenia<sup>2</sup>—but we use the term postviral fatigue syndrome as this draws immediate attention to its two cardinal features.

The disorder was originally noted as occurring as epidemics, but it is now clear that it is an endemic illness with periodic epidemics.<sup>3</sup> Despite exhaustive analysis no causal agent has been identified.<sup>3</sup> Small outbreaks in Scotland in the early 1980s, however, suggested coxsackie B viruses as possible agents because increased serum antibody titres were detected in many patients.<sup>8,9</sup> However, this is only indirect evidence as these viruses are common in the community. A more recent study disclosed chronic excretion of enterovirus in stools in 22% of a group of patients with the postviral fatigue syndrome.<sup>10</sup> Other viruses—for example, varicella-zoster virus, hepatitis B virus, and Epstein-Barr virus—have been implicated.<sup>3</sup>

A preliminary investigation to detect enterovirus specific RNA sequences in samples of muscle from patients with the postviral fatigue syndrome disclosed that a fifth of the 96 cases tested were positive with a nucleic acid hybridisation technique.<sup>11</sup> With the advent of the highly sensitive polymerase chain reaction it is possible to examine for low copy numbers of nucleic acid sequences in cells and tissues.<sup>12</sup> The technique is at least one thousandfold more sensitive than previous hybridisation protocols, and background hybridisation associated with enteroviral complementary DNA probes is eliminated. We used the polymerase chain reaction to search for the presence of enteroviral RNA sequences in a well characterised group of patients with the postviral fatigue syndrome.

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